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# Of postulates and peccadilloes: Robert Koch and vaccine (tuberculin) therapy for tuberculosis

93-22756



Donald S. Burke

*In August 1890, Robert Koch dramatically announced that he had discovered a cure for tuberculosis, and the world rejoiced. The miracle substance was subsequently revealed to be tuberculin, inoculated as a 'vaccine therapy'. However, within a matter of months his claims were disputed and debunked, and his reputation was grievously damaged. The nationalistic pressures, professional jealousies and pecuniary interests that drove Koch's premature announcement are reviewed here and discussed in a context relevant to the development of therapeutic vaccines for human immunodeficiency virus infections.*

**Keywords:** Koch; vaccine therapy; tuberculosis; HIV

'Vaccine therapy', or 'active specific immunization with microbial-derived antigens' for treatment of chronic infections has been an intellectually appealing scientific strategy for over a century (reviewed by the author in Ref. 1). Most physicians today, trained in the antibiotic era, are completely unaware of just how commonplace vaccine therapy was in the early twentieth century: vaccines were used to treat all types of chronic infections, from staphylococcal skin infections to typhoid fever. In the mid-1920s autogenous or stock bacterial vaccines were routinely used for therapy by over half of all internists in the United States. Eventually vaccine therapy faded from clinical practice, but only after the Second World War and the discovery and marketing of potent antibiotics like penicillin and chloramphenicol.

Recently our research group at the Walter Reed Army Institute of Research has been exploring 'vaccine therapy' as a treatment for human immunodeficiency virus (HIV) infections<sup>2</sup>. We have found, in studies of asymptomatic early-stage HIV-infected patients, that repeated inocu-

lations of a vaccine composed of the HIV envelope protein can boost antibody titres and the cellular proliferative responses.

We and other research groups are now in the midst of large prospective, randomized, placebo-controlled efficacy trials. Will future decisions about clinical implementation of HIV vaccine therapy be made on firm, carefully considered scientific analysis of these studies? To what extent might polities, profit and personalities dominate and divert the deliberations?

Koch's tuberculin 'vaccine therapy' debacle of a century ago, recounted in some detail here, stands as a cautionary history lesson.

## BACKGROUND

In 1882, at the age of 39, Robert Koch discovered the tubercle bacillus, and subsequently developed 'Koch's postulates', the cautious, carefully crafted canon for establishing the pathogenic character of a microbe.

Eight years later, before a gathering of 8000 at the Tenth International Medical Congress in Berlin, Koch announced that he had discovered the cure for tuberculosis! The announcement was received with immediate worldwide jubilation, and he was showered with honours and decorations. Yet within a matter of months the claim was disproved and debunked, and Koch's reputation as a medical scientist was sullied. Why? What possessed Koch to proclaim a cure so prematurely, and so publicly?

## CHRONOLOGY OF THE ESSENTIAL FACTS<sup>3\*</sup>

### 3 August 1890

On 3 August 1890, Robert Koch delivered an invited lecture entitled 'On Bacteriological Research' to the

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The views and positions presented in this article are those of the author and do not purport to reflect those of the US Department of the Army or the US Department of Defense

\* The account presented here was constructed directly from Robert Koch's publications and related materials. For a parallel discussion of these events, presented in the context of a full biography, the interested reader is referred to Ref. 3.

International Congress<sup>4</sup>. After a scholarly tour through the then young science of bacteriology he went on to say:

Until now I have intentionally left one question unexamined although it is precisely the one most often asked of bacteriologists ... 'What has been achieved by all the arduous labour that has been invested in the examination of bacteria?'

He then reviewed his own futile research to find an antituberculous antiseptic that was safe and effective in experimental animals. Not until the last few words of his lecture did he reveal his success.

In spite of these failures, I continued the quest and *I ultimately found substances that halted the growth of tuberculosis bacilli not only in test tubes but also in animal bodies*. As everyone who experiments with tuberculosis finds, investigations of the disease are very slow; mine are no exception. Thus although I have been occupied with these attempts for nearly one year, my study of these substances is not yet complete. I can only communicate that *guinea-pigs, which are known to be particularly susceptible to tuberculosis, if subjected to the operation of such substances, no longer react when infected with tuberculosis bacilli, and that in guinea-pigs in which tuberculosis has already reached an advanced stage, the disease can be completely halted without otherwise harming the body*. At this time I conclude only that it is possible to render harmless the pathogenic bacteria that are found in a living body and to do this without disadvantage to the body. Previously, this possibility had been questioned.

However, the further hopes associated with these attempts may be fulfilled - it may be possible, given an infectious disease, to master the microscopic yet previously uncontrollable invaders within the human body. If so, I do not doubt that it will soon be possible to achieve the same results for other diseases...

My only reason for departing from my previous custom by reporting investigations that are not yet complete is to provide added incentive for additional attempts in this area.

Allow me, therefore, to conclude this lecture with the wish that the strengths of all nations may be measured in this field of labour and in war against the smallest but the most dangerous enemies of the human race, and that in this struggle, for the good of all humanity, the success of each nation may repeatedly surpass that of the others. (Italics added.)

That was it. Two sentences, fewer than four score relevant words. Nothing about the nature of the miracle substance, no real data on animal experiments, and no mention of human trials.

Nevertheless, explicit claims were made that (a) the substance was effective both *in vitro* and *in vivo*, (b) it protected naive guinea-pigs against challenge, and (c) it cured tuberculous guinea-pigs. Also, speculation was specifically put forth that (d) the substance would also probably be effective in humans.

#### 15 November 1890

Koch then remained silent on the subject for several months, until 15 November 1890, when the *Deutsche Medizinische Wochenschrift* published the eagerly anti-

pated paper - a three-page note entitled 'A further communication on a remedy for tuberculosis'. In the introductory paragraph of this paper, Koch relates that:

It was originally my intention to complete the research ... before publishing anything on the subject. But, in spite of all precautions, too many accounts have reached the public, and those in an exaggerated and distorted form, so that it seems imperative, in order to prevent all false impressions, to give at once a review of the position of the subject at the present stage of inquiry. It is true that this review can, under these circumstances, be only brief, and must leave open many important questions.

After gracious thanks are extended to his colleague, assistants and clinical collaborators, 13 issues are addressed, one paragraph each, respectively entitled: Nature and physical character of the remedy; Manner or use of the remedy; Effect of injections in healthy individuals; Specific action on tuberculous processes; The local and general reaction to the remedy; The diagnostic value of the method; The curative effect of the remedy; Its action on tuberculous tissue; The dose; The treatment applied to lupus; The treatment applied to tuberculosis of the bones and joints; The treatment applied to phthisis; and Effect in advanced cases of phthisis.

The nature of Koch's cure was the subject of intense curiosity, but this paper offers absolutely no clue as to the identity of the substance:

As regards the origin and the preparation of the remedy I am unable to make any statement, as my research is not yet concluded; I reserve this for a future communication. The remedy is a brownish transparent liquid...

Koch relates that the remedy is ineffective when administered orally, and must be injected subcutaneously, preferably in the back between the scapulae (because local reactions are mildest with injections at this site). He had safety tested the remedy on himself, as a normal control, and found that 0.25 ml evoked a severe systemic reaction with a fever of 39.6 C, chills, aching and vomiting; the site of the injection remained painful and red for several days. Tests in other healthy adult Prussians revealed that normal persons had minimal or no generalized symptoms with a dose of 0.01 ml (delivered as 1 ml of a 1:100 dilution). In contrast, patients with clinically apparent tuberculosis invariably reacted to doses of  $\leq 0.01$  ml. The systemic reaction usually began 4 to 5 hours after the injection, and lasted from 12 to 15 hours.

Koch reported that inflammatory reactions were marked in tuberculous tissues, whereas normal tissues were not appreciably affected:

These local reactions can best be observed in cases where the tuberculous affection is visible; for instance in cases of lupus: here changes take place which show the specific antituberculous action of the remedy to a most surprising degree. A few hours after an injection into the skin of the back, that is in a spot far removed from the diseased spots of the face, etc., the lupus spots begin to swell and redden, and this they generally do before the initial rigour. During the fever, swelling and

redness increase, and finally reach a high degree, so that the lupus tissue becomes brownish and necrotic in places... After the subsidence of the fever the swelling of the lupus tissue decreases gradually, and disappears in about two or three days...

In the 'Diagnostic Value' section, Koch emphasizes again that a systemic reaction occurs in response to a dose of 0.01 ml 'in all cases where a tuberculous process was present in the organism'. He also comments that the tuberculous nature of a given lesion can be confirmed by the inflammatory reaction evoked in response to inoculation. Remarkably Koch does not comment on the local reaction at the site of *inoculation* as having any diagnostic significance.

The mechanism of 'its action' is unclear, but:

...there is no question of a destruction of the tubercle bacilli in the tissues, but only that the tissue enclosing the tubercle bacilli is affected by the remedy ... the remedy does not kill the bacilli, but the tuberculous tissue, and this gives us clearly and definitely the limit that bounds the action of the remedy. It can only influence living tuberculous tissue; it has no effect on dead tissue, as, for instance, necrotic cheesy masses, necrotic bones, etc.

For maximal effect, the remedy must be repeated several times, preferably as soon as the systemic and local reactions from the previous inoculation have subsided; the dosage in successive inoculations can be rapidly increased.

Koch relates what he believes to be convincing therapeutic successes with the remedy in treatment of lupus and bone tuberculosis, particularly in mild or recent cases. Patients with pulmonary tuberculosis (phthisis) were 'much more sensitive to the remedy ... we were obliged to lower the dose'. The effect in cases of phthisis:

...generally showed itself as follows: Cough and expectoration generally increased a little at the first injection, then grew less and less, and in the most favourable cases entirely disappeared; the expectoration also lost its purulent character, and became mucous. ... Within four to six weeks patients under treatment for the first stage of phthisis were all free from every symptom of disease.

In advanced cases of pulmonary tuberculosis, particularly with those with complications such as cavities, early results were not impressive, and Koch does not express enthusiasm for the remedy's use in such cases. He asserts that 'the proper subjects for treatment are patients in the initial stage of phthisis, for in them the curative action can be most fully shown'. Indeed, Koch's passionate belief in the value of the remedy for early disease comes out forcefully:

A doctor who shall neglect to diagnose phthisis in its earliest stage ... will be guilty of the most serious neglect of his patient, whose life may depend on this diagnosis and immediate application of the specific treatment in consequence thereof.

As in his first public report on the new therapy (his oral address in August), Koch again provides little of what could be considered 'hard data' in this, his first written report on the topic. Once again, no clues are given as to the nature of the substance. Again, the report contains no data on animal experiments. While this time Koch does provide considerable clinical information on humans, it is delivered in a remarkable anecdotal style, with essentially no numerical data. As a justification for this peculiar expository style, he related:

I have purposely omitted statistical accounts and descriptions of individual cases, because the medical men who furnished us with patients for our investigation have themselves decided to publish the description of their cases, and I wished my account to be as objective as possible, leaving to them all that is purely personal.

#### 16–18 November 1890

Immediately following publication of his paper<sup>5</sup>, Koch's assistants Drs Pfuhl and Libbertz and his clinical colleagues Drs Brieger, Levy, Frantzel, Kohler and von Bergman conducted an orchestrated series of daily exhibitions at which the method of treatment was demonstrated and patients at various times post-treatment were presented for examination<sup>6,7</sup>. The general points made in Koch's paper were underscored at these conferences.

#### 15 January 1891

Next, Koch published another short paper in the *Deutsche Medizinische Wochenschrift* entitled 'Continuation of the Announcement Concerning a Cure for Tuberculosis'<sup>8</sup>. He begins the paper with a brief but very general overview of clinical trials to date, from which he concludes:

I can only say that everything that I have observed recently, is in complete agreement with that which I had observed earlier, and that I do not feel compelled to change anything in my earlier reports...

and continues

Now that the verification has been completed ... this leads to the necessity of the next step: To study the drug beyond the present area of implementation and discover its principles, which could eventually show how to use this type of treatment in conjunction with other ailments. This task of course requires complete knowledge of the substance at hand. Therefore, I feel the time has come to make a full report of all the necessary information...

Before discussing the drug itself, Koch diverts briefly to present a sketch of his guinea-pig experiments that led to development of the approach. He describes the now classical 'Koch phenomenon' which occurs when an infected animal is reinoculated with tubercle bacilli:

...a rather strange process begins after a time period of about 2 or 3 days. The area becomes hard and changes to a darker colour... Over the next few days, it becomes apparent that the skin has become necrotic ... Thus the infected tubercle bacilli cause a different

reaction in a healthy guinea-pig as opposed to one which was previously infected with tuberculosis. This conspicuous effect does not only occur in the case of living tubercle bacilli, but also in the case of dead bacilli... After these strange facts were discovered, I followed them in all directions...

Koch observed that killed bacilli in the guinea-pig inoculations were not absorbed or dispersed, but remained locally unchanged. From this observation he deduced that:

[the mechanism by] which this method of treatment has a therapeutic effect on the tuberculous process, must therefore have a soluble consistency... Thus it was merely a case of trying to identify the process which occurred within the body so that it could be conducted outside of the organism and if possible to extract the curative and effective substance... This task cost a great deal of time and trouble.

and he went on to announced (italicized in the original German, also):

*Consequently, the substance, with which the new therapeutic treatment for tuberculosis is performed, is a solution of a suspension of glycerin and extracts from tubercle bacilli cultures.*

He discusses properties of the active ingredient relevant to its purification, particularly its alcohol insolubility, and deduces:

For use in the practical sense this new distillation does not have any prominent advantages over the glycerin solution, because the human organism is completely indifferent to the substances that have been filtered out. Consequently the further cleaning of this substance would merely unnecessarily add to the cost...

Koch presents in this paper his first theoretical explanations for his observations, preceded by a modest expression of uncertainty 'I submit, without maintaining that my theory is the best explanation, the following hypothesis...'

The tubercle bacilli produce through their growth certain substances, which in the living element of their surroundings, influence the cells in a distinct manner, indeed negatively so. Among them is a particular substance, which in a certain concentration, kills living protoplasm and changes the surrounding area into, as it was described by Weigert, a coagulation-necrosis. Through this necrotic state of the surrounding tissue, the tubercle bacillus finds a rather undesirable nutritional environment, such that it does not continue to grow, and in some cases dies... If one were to artificially increase the amount of necrosis-producing substance in the tissue surrounding the bacillus, then the necrotic area would expand to a greater distance, which in turn would negatively influence the environment for nourishment for the bacillus...

## 22 October 1891

Not until 22 October 1891, in an article in the *Deutsche Medizinische Wochenschrift* entitled 'Additional

information about tuberculin', did Koch present details about the preparation, purification and chemical composition of the new therapy (which he now called 'tuberculin')<sup>9</sup>. He commented that in preliminary experiments the effective substance in tuberculin was found to be a protein or a protein-like substance, and expressed his concerns that it might be difficult to 'isolate the substance without changing its properties through the method of manipulation used'. In order to do so, it was first necessary to devise a reliable bioassay that could be used to monitor biological activity. In his words:

Without a step by step control of the situation, one soon loses the path of the experiments and one tends to digress from the original experiment's purpose.

Koch provides some details about the tuberculous guinea-pig model that he employed as a bioassay. He rejected systemic signs or local reactivity as endpoints, because 'the increase in temperature and the local symptoms in the guinea-pig are not pronounced enough'. He instead used death of the guinea-pigs as an endpoint, and expressed the tuberculin bioactivity as the amount in grams necessary to kill animals infected 4-5 weeks previously. He then discusses some of the problems in deciding if the death of a guinea-pig is directly related to the tuberculin injection, and suggested that 'haemorrhage-like spots on the surface of the liver' was a reliable, almost pathognomonic sign. To be attributable to tuberculin, the death must occur between 6 and 30 hours after the inoculation.

Koch tried various methods to isolate the active component of tuberculin. He found that a 60% alcohol precipitate of crude tuberculin yielded a clean, water-soluble, active substance. However, this purified product tended to be unstable, and lost potency over only a week or two. If prepared as a solution of pure tuberculin in 50% glycerin, the product was quite stable. He analysed and reported on the chemical properties of the purified product, and found the ratios of carbon, hydrogen, nitrogen and sulfur to be 48, 7, 14 and 1% respectively; ash (mineral) content 17 to 20%. Having isolated an active substance that was 50-fold purified over the crude material, he then proceeded to test the purified tuberculin in humans. It was hoped that the therapeutic effect seen with unpurified product could be seen, but 'without any of the distracting and uncomfortable side effects'. Several persons volunteered to be injected with the new purified product lots including his colleagues Kitasato and Wassermann. To Koch's profound disappointment all had severe reactions:

... all of the known side effects that we had experienced after the untreated tuberculin injections were exhibited ... we were unable to prove any difference in this property between the treated and untreated tuberculin.

Subsequent trials in tuberculous patients led to a similar observation that treated and untreated tuberculin did not vary significantly in their effects. He went on to conclude that:

Interesting and important as the experiments in the purification of the effective principle of tuberculin are in theory, in a practical sense we have not made much progress.

Koch concludes this paper with a discussion of methods for large-scale cultures of mycobacteria. In order to alert others who might try the process, he stresses the importance of being 'completely certain that ... all of the tubercle bacilli without exception have been killed'. This he accomplished by heat (several hours at near 100°C in the evaporation process) and subsequent filtration through kaolin. He also points out the requirement that the cultures must be completely pure 'which must be verified through a microscopic examination of each individual container'. Lastly, the product 'must be tested for its potency' in tuberculous guinea-pigs.

### JUBILANT PUBLIC REACTION

Koch's initial announcement in August 1890 on the 'cure' for tuberculosis was delivered in grand style at the Tenth International Medical Congress in Berlin. Prussia hosted the event, and provided a suitably Olympian setting: the huge auditorium that seated the 8000 delegates from around the world was specially adorned as an imitation Temple of Zeus<sup>10</sup>. Rumours had abounded that Koch would reveal a momentous discovery. The crowd listened expectantly, and they were not disappointed.

The reaction to Koch's report was instantaneous and electric. Despite his own modest claims, word of a 'cure' promptly spread worldwide, and consumptives began to converge on Berlin.

Europe witnessed a strange but not unprecedented spectacle last month. In the Middle Ages the discovery of a new wonder-working shrine, or the establishment of the repute of the grave of a saint as a fount of miracles, often led to the same rush which has taken place last month to Berlin ... the dying have hurried thither, sometimes to expire in the railway train, but buoyed up for a time by a new potent hope...<sup>11</sup>

Indeed, the rush to Berlin created what was believed to be a 'serious danger to the public health of this city likely to arise from the sudden invasion of patients suffering from every form of tuberculosis and coming from all the corners of the earth'<sup>12</sup>.

The *London Review of Reviews* featured a cover cartoon with 'Koch as the new St George' slaying the tubercle bacillus. In the feature article Arthur Conan Doyle, the physician-author of *Sherlock Holmes* stories, characterized Koch the man thus<sup>13</sup>:

Some five feet and a half in height, sturdily built, with brown hair fringing off to grey at the edges, he is a man whose appearance might be commonplace were it not for the vivacity of his expression and the quick decision of his manner.

The rich and famous immediately sought the cure. Lister sent his niece to Berlin to be treated, and Ehrlich, later a Nobel laureate but then an assistant to Koch, became a patient<sup>12,13</sup>. Conan Doyle noted a pile of letters four feet wide and two feet deep on the floor of Koch's office, all pleading for the miracle cure.

One American participant<sup>14</sup> at the International Congress wrote home that:

... listening to the papers of these intellectual giants, one could divine that a great tidal wave in science was

imminent and that it centered upon the discovery of Koch.

### SCIENTIFIC SCEPTICISM AND SUSPICIONS

While the lay press celebrated, hints of disbelief and disgruntlement began to appear in the medical scientific literature. Take, for example, this sober *Lancet* editorial response<sup>15</sup> to Koch's unprecedented (and undocumented) August 1890 announcement:

Indeed, apart from the fact that we may be on the verge of a revolution in therapeutics, it may be said that bacteriology itself is on its trial in this momentous investigation.

Many reserved judgement simply because it was the great Robert Koch who promised a cure on the horizon:

Such a statement from many another source would have been received with more than incredulity, but this announcement, when made at the International Medical Congress, was welcomed as 'glad tidings of great joy', for it was generally felt that Robert Koch was a man who seldom made a statement which he could not justify... (Ref. 16)

and

he would be the first to deprecate either haste in drawing conclusions or a premature adoption of a method on which so much depends. (Ref. 15)

Koch's peculiar secretiveness about the exact nature of the therapy raised doubts. Speculations about pecuniary interests surfaced immediately:

It was at one time reported that the Emperor, who has had an interview with Professor Koch, has been so impressed with the value and importance of the discovery as to intend to give Professor Koch 100 000 pounds ... this, however, does not appear to be the case. (Ref. 17)

and

Amongst the many rumours that have been current of late, there has been one which seems to point to the intention of the German Government to retain, as it were, the monopoly of the remedy in its own hands, or, in other words, to become the proprietor of a vast patent-medicine factory. (Ref. 16)

Most of the information about the new therapy available outside Berlin was provided by foreign correspondents or by physicians who had travelled there to learn more about the treatment first hand. Sir Joseph Lister visited in the late autumn, and reported<sup>12</sup>:

The effects of this treatment upon tubercular disease are simply astounding ... while Koch's fluid has this searching diagnostic value, there can be no doubt that it has also a powerful therapeutic or curative influence ... I must say that the carping against Koch on account of what is spoken of as a 'secret remedy' can

only proceed from absolute ignorance of the beautiful character of the man.

Although Koch was secretive about the preparation and composition of his therapy, he promptly provided small aliquots to certain esteemed physicians, mostly in Prussia but also throughout the world. A sceptic might have difficulty deciding if this parallel effort was an admirable gesture of international scientific cooperation or simply a marketing ploy, but nonetheless, within weeks after Koch and his close clinical colleagues completed their first human trials, small quantities of the therapy were widely distributed. For example, on 22 November 1890, Drs Heron and Cheyne announced in London<sup>18</sup>:

Professor Koch has requested us to demonstrate in London his method of treatment of tuberculosis, and has supplied us with a small quantity of fluid for this purpose... We may state that as the amount of fluid at present available is very small, Professor Koch has only been able to supply us with a quantity sufficient for the purposes of this demonstration.

Some British medical men of the day resented the circus atmosphere that seemed to surround these demonstrations<sup>19</sup>:

Day after day the gaping multitude were informed how Dr This and Dr That, having received a sample of the precious fluid, had proceeded to inject it in the presence of a circle of admiring and envious confrères. The ceremonial, which might have been the performance of a sacred rite rather than the administration in minimal doses of hypodermic injections of a secret remedy was... chronicled with as much detail as a fashionable wedding or a public funeral.

In France the reception of Koch's discovery was initially cool but cordial. Demonstrations by Drs Cornil and Chantemesse confirmed the general observations of a systemic reaction and local inflammation, but enthusiasm was giving way to uncertainty because the effects in pulmonary cases were felt to be minimal<sup>20</sup>. *La Provence Médicale* was particularly critical, attacking:

...the decision of the German Government to take over the monopoly of the 'lymph' as it were on a par with alcohol or tobacco, and say it is clear that in this it has but one object - viz., to make money. Hitherto this kind of thing has been left to charlatans and has been discredited in France, Germany, and England: but now we see a nation descending to the level of purveyors of secret remedies... Koch's position is regarded with pity, for although laden with honours, he is in danger of losing his claims to be regarded as a benefactor of humanity in becoming a trademark for a German product. (Ref. 21)

Pasteur sent a polite and proper congratulatory telegram<sup>22</sup> to Koch, but otherwise stayed out of the fray:

M. Pasteur and the heads of the departments of the Pasteur Institute send to Robert Koch all their best congratulations for his great discovery.

In America as well, some believed that the emperor had no clothes. The editorial policy of the *Journal of the American Medical Association* was mocked in one letter<sup>23</sup>:

Think of it! Thousands of physicians - Germans, Austrians, Italians, Russians, English, and Americans flocking to Berlin to see Professor Koch's treatment, scrambling for places, and offering fabulous prices for a few drops of the liquid whose composition they do not know and cannot find out! And when asked why they want it, reply, 'Because Koch thinks it will cure tuberculosis!' When has the practice of medicine witnessed such a spectacle? And the JOURNAL'S praise of Koch's wisdom is helping to swell this crowd.

The Director of the New York Bacteriologic Institute, Dr Paul Gibier, who had received 'a certain quantity of Koch's lymph', though less exclamatory, was no less damning in his assessment<sup>24</sup>:

We are... assisting at the spectacle of one of the greatest medical and scientific delusions that has ever existed.

The turning point in the debate over the effectiveness of tuberculin therapy came in early 1891, when the *Klinisches Jahrbuch* published a voluminous report summarizing clinical studies in Prussia conducted between September 1890 and January 1891<sup>25</sup>. The compendium was sponsored by the Government, and was edited by Professor Guttstadt, a Professor of Medical Statistics. It included reports of 55 clinical studies with a total of 2172 patients. The total number of injections was over 17 500 with the greatest number in one case being 54. The volume contained reports from several Prussian physicians whose names are now immortalized in eponyms: Jolly, Henoch, Trendelenburg, Weber, Quincke and Hippel.

Information was sufficient to assess the effect of the treatment in 1769 cases. Of these, 708 were classified as 'external tuberculosis', a category which for the most part comprised tuberculosis of the skin (lupus), bones and lymph glands. Another 1061 had pulmonary tuberculosis. The clinical responses were classified, somewhat arbitrarily, as cured, substantially improved, improved, unimproved, or died (Table 1). The best results occurred in cases of lupus (tuberculosis of the skin), where 83 of 188 were either substantially improved or cured. Overall, more patients died during the therapy than were cured, and fewer than 20% of all patients treated were considered substantially improved. Most of the deaths occurred in patients with advanced cavitary pulmonary disease.

Tuberculin came to be viewed as dangerous. Systemic reactions in some cases led to delirium, coma or angina

Table 1 Results of treatment with tuberculin

|                        | External<br>tuberculosis | Pulmonary<br>tuberculosis |
|------------------------|--------------------------|---------------------------|
| Cured                  | 15                       | 13                        |
| Substantially improved | 148                      | 171                       |
| Improved               | 237                      | 194                       |
| Unimproved             | 298                      | 586                       |
| Died                   | 9                        | 46                        |

pectoris. Local reactions at the site of tuberculous disease also caused morbidity. According to the *Journal of American Medical Association (JAMA)*<sup>26</sup>:

...the local reaction consists of intense congestion around the tubercular focus, effusion of serum and more or less migration of leukocytes, in short a disturbance verging towards or even identical with severe inflammatory swelling. Under certain conditions such a reaction may prove dangerous if too intense.

Some of the locations where the increased inflammation was thought to be especially dangerous were in tuberculosis of the larynx and tuberculous meningitis. Virchow commented especially on the frequency of catarrhal pneumonia and exceptionally phlegmonous infiltration of the lungs in subjects dying under treatment with tuberculin<sup>26</sup>.

A few days later, another *JAMA* editorial entitled 'The value of Koch's tuberculin'<sup>27</sup> summarized:

The therapeutic results obtained by tuberculin may be summarized in two statements: (1) ... the agent exerts a specific effect on all tubercular lesions, by starting an inflammatory process in and around the tubercular tissue which tends to cure the disease and (2) this reparative change has not proceeded up to the actual cure in the majority of cases hitherto treated.

Thus, by the spring of 1891, the fervour for tuberculin therapy had waned almost completely. The toxicity was simply too great, and the therapeutic benefit too unpredictable and marginal. William Welch<sup>28</sup> conveyed the opinion that:

It seems most gratifying to me that the stage of newspaper notoriety in this matter [vaccine therapy for tuberculosis] has given place to quiet laboratory work....

Despite his best efforts, Koch eventually conceded that he could not dissociate the therapeutic from the toxic components<sup>9</sup>. Other investigators thought they had purified out products with higher therapeutic ratios. Klebs, for example, prepared and distributed a 'cleansed' fraction which he called 'Tuberculocidin', but it was not subsequently proven to have any superior clinical benefits<sup>29</sup>.

Koch continued to experiment with tuberculin therapy for the remainder of his life, including pioneering studies on use of serum bacillus-agglutinating titres to guide vaccine therapy<sup>30,31</sup> (this general strategy was adopted and more fully developed by Sir Almroth Wright in England). In his 1904 Nobel Lecture entitled 'The current state of struggle against tuberculosis' Koch applauded doctors in sanatoria who 'administer tuberculin preparations, in order to achieve swifter, and, in particular, more lasting cures'<sup>32</sup>.

Tuberculin therapy continued to be used in Europe and in the USA throughout the first half of the 20th century. Indeed, textbooks with titles like *Tuberculin and Vaccine in Tubercular Affections: A Practical Guide for the Utilization of the Immune Response in General Practice or A Guide to the Use of Tuberculin* were commonplace in the years around World War I<sup>33,34</sup>. The discovery of

antibiotics with anti-tuberculous activity signalled the demise of tuberculin therapy. However, even as recently as 1950, tuberculin was presented in standard medical texts as a legitimate therapeutic option<sup>35</sup>.

Tuberculin, specific but dangerous, has been relegated to the treatment of ocular tuberculosis, where reactions can be closely observed. It should never be used except by experts, and even then its effectiveness for pulmonary tuberculosis is questionable.

Today, tuberculin is not licensed, used, nor even considered, as a therapy. Indeed, few practitioners are aware that it ever was.

## KOCH'S COMPORTMENT

Koch entered the field of microbiology in 1876 with his work on anthrax; in 1882 he discovered and proved the significance of the tubercle bacillus, and in 1883 he discovered the cholera vibrio<sup>36</sup>. Thus, Robert Koch was already a legendary figure in 1885 when, at the age of 42, he accepted the chair of hygiene at the University of Berlin and simultaneously a position as head of a new Hygienic Institute. Pupils came from every corner of the globe<sup>37</sup>.

Koch's scientific comportment changed during this time; he became secretive, preferring to work in near solitude. Indeed, few of his select students or brilliant colleagues knew the subject of his labours. No-one at his Institute except Koch himself was permitted to do research on tuberculosis<sup>37</sup>. Surprisingly, even as Koch became more withdrawn, research work at his Hygienic Institute accelerated: in 1890 Ehrlich established basic concepts of immunization, and Behring and Kitasato developed antitoxins for diphtheria and tetanus. Behring's exquisite successes in antitoxin clinical trials brought him considerable acclaim, to the extent that he became Koch's rival for leadership within the Institute<sup>38</sup>.

Koch's first guinea-pig experiments with tuberculin were conducted at the Hygienic Institute, but all of the subsequent studies were done by Koch outside his usual official channels:

[He] hired a private house at his own expense, and obtained the assistance of two gentlemen with whom he had private acquaintance - Dr Libbertz, an old school-fellow, and Dr Pfuhl, his own son-in-law. The lymph was prepared in considerable quantities in this private house by these two gentlemen under Dr Koch's supervision, and the earliest injections in man were made in the private hospitals of Drs Cornet and Levy. (Ref. 39)

At some point Koch's superiors in the German Government began to directly influence Koch's decisions about tuberculin. His colleague and friend Professor Waldeyer related that in the days before the August 1890 International Congress Koch was being constantly badgered by government officials to reveal his discovery, and subsequently did so against his own better judgement<sup>39</sup>. Later, acting on the advice of, or perhaps the instructions of, his supervisor von Gossler, the Minister of Education, Koch published his first paper on tuberculin. Shortly thereafter, Koch's private house in which the lymph was manufactured was taken over by

the Education Department, and Drs Libbertz and Pfuhl became government employees<sup>39</sup>. Von Gossler arranged for Koch to retire from his official and his teaching duties so that he might devote himself to his work on tuberculin<sup>40</sup>.

Of course, questions arose over exactly who owned the rights to the discovery. The precedent in Germany was that the discoveries made by teachers in public institutions belonged to the discoverer. However, in this instance, von Gossler<sup>40</sup> felt that:

... owing to the extraordinary demands which had arisen for the remedy ... the remedy should at first be entrusted to men of standing and repute, first of all in Germany, then abroad.

Exorbitant charges were being made by some private practitioners who were using the remedy as demand outstripped supply. Something had to be done. Von Gossler related his and Koch's plans to develop a national institute for clinical and scientific work<sup>40</sup>:

... after consultation with Professor Koch and considering every aspect of the question, he thought the State should take the matter in hand ... provisional arrangements would soon develop into an institution where everything would be definite and satisfactory ... the remedy would be supplied free of cost to all the central medical institutions, so that the poor might derive the full benefit ... Professor Koch would be at the head ... about a half million marks would be required for this work, which would be provided from extraordinary funds. Private generosity had also placed at Koch's disposal one million marks, but Koch was obliged to decline...

### POSSIBLE MOTIVES, NOBLE AND IGNORABLE

Indisputably, the 'tuberculin therapy affair' of 1890-1891 did not go well for Robert Koch. As Elie Metchnikoff bluntly expressed it<sup>41</sup>:

Koch's old admirers cast him down from his pedestal, forgetting all the benefits humanity had derived from his earlier labors.

I offer here a brief discussion regarding 'Why?' How did the previously meticulous Koch, as 'coldly logical as a text-book in geometry' find (put) himself in a position to be discredited and dishonoured?

#### Nationalist pressures

Most medical historians take the position that Koch was pressured by the Prussian government into premature disclosure of his discoveries. For example, Paul deKruif<sup>42</sup> in his romantic *Microbe Hunters*, published in 1926, suggests that Koch was merely a pawn in European realpolitik, that his 'ambitious but well-meaning countrymen' prepared without knowing it:

... a disaster for him, a tragedy that, alas, has partly tarnished [his] splendor ... the authorities were putting pressure on him ... for a big cure, for the glory of the Fatherland, as Pasteur had done for the glory of France ... it was ominous stuff. He listened at last, and who can blame him.

Other, more recent, texts offer similar assessments:

Koch felt the pressure acutely ... the very support he had been receiving from the Prussian government turned into quiet, implicit pressure ... Koch ... allowed his ambition to outrun his judgement. (Ref. 43)

... his official employers wanted to monopolize it for the glory and profit of the Fatherland. The Germans had joined the French in making the new bacteriology a nationalist trophy. (Ref. 44)

While the pressures of nationalism do seem to be one important influence on Koch during 1890-1891, there were certainly others.

#### Professional jealousies

Koch's discovery of the tubercle bacillus in 1882 had elevated him to a stature almost equal to Pasteur. However, the latter's 1885 demonstration of post-exposure prophylaxis of rabies catapulted him closer to the international spotlight, once again eclipsing Koch<sup>37</sup>. There is evidence of substantial chronic enmity by 1890 between Koch (then 47 years old) and Pasteur (then 68 years old and partially paralysed)<sup>45</sup>. It is reasonable to assume that Koch felt envious of Pasteur's rabies success, and that this provided some incentive for his work on a cure for tuberculosis.

Closer to home, Behring (aged 36), who had joined Koch's Hygienic Institute just one year earlier, was already enjoying substantial fame for his work on antitoxins. As Koch withdrew into his tuberculin work, Behring proportionately gained influence, such that his circle of co-workers became an institute within an Institute. Indeed, Behring's co-author on his landmark paper on diphtheria antitoxins was Kitasato, not Koch. Some years later Behring filed a patent application for a tuberculosis immunizing agent which interfered with one submitted by Koch. Although Koch's application was favoured and Behring's disallowed, the episode suggests Behring's truculent attitude towards his former boss<sup>46</sup>. Given this background, it seems likely that Behring's receipt of the first Nobel Prize in Physiology or Medicine (in 1901, four years before Koch received his own in 1905), probably offended Koch. Was this domestic professional rivalry already developing in 1890? Possibly; it might have been another factor in Koch's hasty announcement of a cure for tuberculosis.

#### Personal financial interest

Then as now, the bizarre manner in which Koch announced his discovery - choosing the most visible public forum, yet keeping the essentials secret - fuels speculation that Koch may have been driven by pecuniary interests. While it may be true that he was pressured by nationalistic zealots into a premature announcement, it is equally possible that he was less pressured than seduced. Certainly large sums of money were thought to be at stake.

Notwithstanding Koch's high-minded assertions that he was withholding the formula simply because 'my work is not yet completed', it is difficult to distinguish the potential financial interests of the state from the personal financial interests of Koch himself. Von Gossler's agreement with Koch, that the therapy should be

produced under the management of the state, included arrangements for a new Institute with Koch as its first Director, a significant incentive to cooperate. The *British Medical Journal* reported disapprovingly that:

... it has been said ... Dr Koch and each of his assistants had accepted a large immediate payment, and that they were to receive a royalty upon all sales in the future. (Ref. 43.)

Exact sums of the payments to individuals are not reported, but again; it can be assumed that they were sufficient to provide an incentive for cooperation. In fairness, it must be pointed out that a similar system of rewards for patented inventions is available to present-day government scientists in the United States, but the conditions and amounts are specified by law, not by bargain. Certainly it would be unjust to suggest that Koch had no right to material gain from his labours. Were it not for the shroud of secrecy, only romantic dreamers would criticize Koch on this aspect of the tuberculin affair.

#### **Transitions in his personal life**

In the period around his August 1890 announcement, 47-year-old Koch's personal life was somewhat disordered. He had become estranged from his wife Emmy and he had just developed a relationship with the 18-year-old Hedwig Freiberg (who later became his second wife)<sup>47</sup>. She was fascinated by Koch's studies; when he inoculated himself with tuberculin, she volunteered to be injected too. On a trip to Egypt in the spring of 1891, when the public adulation over tuberculin had turned to scorn, Koch wrote back to Freiberg<sup>48</sup>:

As long as you love me, I cannot be beaten down by the vicissitudes of fate. Do not abandon me now for your love is my comfort...

Koch's subsequent marriage to Hedwig Freiberg was solid and lasting; she accompanied him on many of his adventurous overseas studies in Africa and Asia. However, at the time the relationship was viewed as something of a scandal. Metchnikoff<sup>49</sup> relates that it:

... unleashed a moral storm... During the Congress of German Physicians in 1892, where I was present, Koch's marriage was the topic of all conversations. Koch was exposed to the most serious accusations; his romance certainly interested the professors more than all the reports submitted to the Congress.

Metchnikoff, a life-long comrade of Pasteur, entreats (in my opinion somewhat half-heartedly) the reader to not judge Koch harshly<sup>48</sup>:

In the future, humanity's munificent geniuses will probably be more appreciated than nowadays, and the absurd prejudices which still beset even the most independent spirits shall have vanished. ... Future generations will show much more justice and tolerance towards Koch in this matter than his own contemporaries. It is desirable that a great man's private life not be covered up with a veil by his biographies.

Was Koch suffering a 'mid-life crisis' in 1890, and was

this associated with his premature announcement of a cure? This, too, seems to be a viable interpretation.

#### **HOW CLOSE TO A CURE?**

Clearly Robert Koch fervently believed in the curative properties of tuberculin. However, despite decades of effort, he never developed real proof for the efficacy of tuberculin ('vaccine') therapy. Was Koch simply deluded and misguided? Or was his obstinate scientific unorthodoxy in this matter yet another manifestation of his genius?

There seems to be little doubt, based on the clinicopathological observations of Koch, Lister, Virchow and others, that tuberculin therapy incited an increased inflammatory response in tuberculous tissues remote from the inoculation site. Experimental studies in tuberculous guinea-pigs, reported by Trudeau and others, provided additional evidence. However, it is not possible to determine from these reports if the tuberculin effect was truly antigen-specific; it is possible that the observed inflammatory effects in remote tissues were mediated through non-specific immunostimulatory mechanisms.

Regardless, Koch's observations on the effects of the therapy were extraordinarily precise. Through his tuberculin therapy studies, he anticipated much of our current understanding of tuberculosis immunity. For example, Dannenberg, in a recent review<sup>50</sup>, explained that:

... when cell-mediated immunity is powerless to stop intracellular bacillary growth, the host uses delayed-type hypersensitivity to cause caseous necrosis. In other words, by killing the non-activated macrophages in which the bacilli are growing, the host eliminates the intracellular environment that is so favourable for growth.

Koch's wording in his November 1890 paper<sup>5</sup> is remarkably similar, and anticipates the role of delayed-type hypersensitivity at the cellular level:

... there is no question of the destruction of the bacilli in the tissues, but only that the tissue enclosing the tubercle bacilli is affected by the remedy ... the remedy does not kill the bacilli, but the tuberculous tissue.

Why was Koch unable to develop these brilliant observations fully into a clinical cure? One main reason was the complexity and impurity of his 'tuberculin' preparations - he could never make a preparation that retained the therapeutic effect while eliminating the toxic properties. This comes as no surprise, for even today, using modern molecular biology techniques, it has not been possible to determine which antigens and epitopes are critical for immunity<sup>50</sup>. Another major reason for Koch's failure was the anecdotal, uncontrolled design of his clinical studies, unfortunately typical of the era.

Of course, it is possible that 'vaccine therapy', or 'active specific immunization with microbe-derived antigens', may *never* be effective in the treatment of chronic infectious diseases. Recent clinical trials analogous to those of Robert Koch, in which subcutaneous inoculations of irradiation-killed *Mycobacterium vaccae* bacilli were used to treat patients with pulmonary tuberculosis, have shown only mixed results<sup>51</sup>. While it

is true that the efficacy of vaccine therapy has not been proven for any clinically manifest human infectious disease, there are now, however, substantial encouraging data from modern studies of leprosy, leishmaniasis and herpes simplex infections, as well as from our own studies on HIV<sup>1,2</sup>.

## CONCLUSION

Rational scientific analysis took a back seat to nationalistic pressures, professional jealousies, profit motives and personalities when Robert Koch prematurely announced to the world in 1890 that he had invented a cure for tuberculosis, tuberculin vaccine therapy. It is to be hoped that now, a century later, decisions about HIV vaccine therapy will be made so as to better serve the public interest.

## AUTHOR'S NOTE

All seven of Koch's publications on tuberculin and tuberculin therapy were originally published in German (Refs 4, 5, 8, 9, 30, 31 and 32). Of these, complete English translations of two have been published, Koch's original 1890 International Medical Congress address and his 1905 Nobel Prize acceptance speech (Refs 4 and 32). A partial English translation of Koch's January 1891 *Deutsche Medicinische Wochenschrift* article<sup>8</sup> has also been published. German-to-English translations for this paper were provided by D. Haertl. The author offers to make available English translations of all seven articles. Interested parties should send requests directly to D.S.B.

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